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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/215,163	12/18/1998	JEFFREY R. STINSON	04995.0032-0	7721

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	**PAPER NUMBER**
1645	22

DATE MAILED: 09/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/215,163	Applicant(s) STINSON ET AL.	
	Examiner Robert A Zeman	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,13-20,23,29 and 32-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,13-20,23,29 and 32-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 6-21-2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/215,163 is acceptable and a CPA has been established. An action on the CPA follows.

The amendment and response filed on 6-21-2002 is acknowledged. Claims 30-39 have been added and renumbered 32-41, respectively in accordance with § 1.126 that states:

> The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled the remaining claims must not be renumbered. When claims are added, they must be numbered by the applicant consecutively beginning with the number next following the highest numbered claim previously presented (whether entered or not). [32 FR 13583, Sept. 28, 1967; revised, 62 FR 53131, Oct. 10, 1997, effective Dec. 1, 1997].

Claims 1-2, 13-20, 23, 29 and 32-41 are pending and currently under examination.

Claim Rejections Withdrawn

The rejection of claims 1, 13-20, 23 and 29 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a monoclonal antibody that binds to Shiga Toxin I, but does not reasonably provide enablement for humanized monoclonal antibodies that bind shiga toxin type 1 variants or fragments or derivatives is withdrawn. Said rejection, as it still applies to the newly amended claims is incorporated in the rejection outlined below.

New Objections

Claim 32 is objected to because of the following informalities: "humanize" is misspelled. Appropriate correction is required.

Claim 34 is objected to because it starts with an improper article. Dependent claims should start with the article "the". Appropriate correction is required.

New Grounds of Rejection

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 41 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to monoclonal antibodies 13C4 and 11E10.

Claims 1-2, 13-20, 23, 29 and 32-41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 in view of Carter et al. (WO 94/04679). O'Brien et al. also teach the use of 11E10 monoclonal antibody of the IgG1 subclass with a kappa light chain and monoclonal antibody 13C4 (see column 4, lines 10-19 and lines 38-58). Carter et al. disclose methods of producing

humanized chimera antibodies (see page 5). Said antibodies do not cause the formation of anti-mouse immunoglobulin antibody in the body of a patient and therefore side effects are reduced (see page 4).

Since the amino acid sequence is an inherent property of any protein it would have been *prima facie* obvious for one of skill in the art at the time the invention was made to synthesize and express the humanized chimera antibodies which bind to shiga toxins utilizing the methodology of Carter et al. One of ordinary skill in the art would have been motivated to humanize the monoclonal antibodies taught by Speirs et al. and O'Brien et al. in order to avoid the side effects by anti-mouse immunoglobulin antibody when said antibody is administered, yet still maintain an effective therapeutic effect. One would have had a high expectation of success since the process of humanizing a known antibody is well known in the art, particularly one directed to a human pathogen.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 13-20, 23, 29 and 32-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized monoclonal antibodies based on monoclonal antibodies 13C4 or 11E10, does not reasonably provide enablement for any other humanized antibodies that binds to shiga toxin proteins. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification discloses humanized monoclonal antibodies based on monoclonal antibodies 13C4 and 11E10 (H13C4 and H11E10). Additionally the specification discloses the use of portions of SEQ ID NO:42 and SEQ ID NO:44 in the variable light and heavy chains, respectively, of said humanized antibodies. While, the specification states "substitutions, additions or deletions may be made to the sequence encoding the antibody"; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the resulting antibody. Further, it is unpredictable as to which amino acids could be added and which could be removed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be safely made which a reasonable expectation of success are limited. Some positions are critical to the proteins structure/function relationship, e.g., such as the regions involved in binding or catylization and can tolerate very little or no changes to their sequence. Any change to the primary sequence can affect the correct three-dimensional special orientation of the protein's catalytic or binding sites. In the instant case a single substitution could totally ablate the ability of a given antibody to bind a shiga toxin protein. It is equally possible that a single substitution could prevent the proper chain assembly of a chimeric antibody. The specification has failed to set forth the location (or sequence) of the immunogenic epitopes. The specification merely outlines, in great detail, the materials and methods needed for to make humanized antibodies based on the 13C4 or 11E10 monoclonal antibodies. Given the lack of guidance contained in the specification and the unpredictability in determining acceptable

amino acid deletions, additions or substitutions, one of skill in the art could not make the broadly claimed invention without undue experimentation.

Claims 23 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising humanized monoclonal antibodies based on monoclonal antibodies 13C4 or 11E10, does not reasonably provide enablement for any other humanized antibodies that bind shiga toxin proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The aforementioned claims are drawn to pharmaceutical compositions. The specification, however, is silent on how such a composition would be used and equally silent on the efficacy of said compositions. People of skill in the art require documented factual evidence that a benefit can be derived by the therapeutic application of a substance. The instant specification fails to provide evidence that the claimed pharmaceutical compositions would elicit any type of beneficial therapeutic response. Since no evidence has been provided that illustrates or even suggests that the claimed pharmaceutical compositions are capable of eliciting a beneficial therapeutic response, one of skill in the art would not be able to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-18, 29 and 32-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13 and 17 are rendered vague and indefinite by the term "Shiga toxin type 2 variants". It is unclear what is encompassed by the said term. What constitutes a "variant"? How much divergence from the wild-type toxin must there be in order to be considered a "variant? At what point does a "variant" toxin become an unrelated protein? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claim 15 is rendered vague and indefinite by the use of the term "is from the sequence set forth in SEQ ID NO:42 and SEQ ID NO:44". It is unclear what is meant by said term. Is applicant claiming that a given variable region must contain part of **both** SEQ ID NO:42 and SEQ ID NO:44? It is suggested the said claim be amended to recite " at least part of said variable region is set forth in SEQ ID NO:42 or SEQ ID NO:44

Claim 20 is rendered vague and indefinite by the language used and the organization of the claim. It is unclear what is meant by the phrase "variable region contains at least part of the CDR sequences located as follows...". Additionally, it is unclear whether SEQ ID NO:44 is meant to identify all recited heavy chain CDRs or just CDR2. It is equally unclear whether SEQ ID NO:42 is meant to identify all recited light chain CDRs or just CDR2.

Claim 32 is rendered vague and indefinite by the use of the phrase "comprises amino acid sequences". It is unclear whether said term refers to a plurality of sequences as implied by said term or a single sequence as described by the Markush group recited in said claim.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 13-20, 23, 29 and 32-41 rejected under 35 U.S.C. 103(a) as being unpatentable over Speirs et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Carter et al. WO 94/04679).

Speirs et al. disclose the use of the 11E10 monoclonal antibody that binds to shiga-toxin II and the 13C4 monoclonal antibody that binds Verotoxin 1 (see abstract and page 651, first column).

O'Brien et al. also teach the use of 11E10 monoclonal antibody of the IgG1 subclass with a kappa light chain (see column 4, lines 10-19 and lines 38-58).

Neither Speirs et al. nor O'Brien et al. disclose the sequences (either DNA or amino acid) of the 13C4 or 11E10 monoclonal antibodies.

Carter et al. disclose methods of producing humanized chimera antibodies (see page 5). Said antibodies do not cause the formation of anti-mouse immunoglobulin antibody in the body of a patient and therefore side effects are reduced (see page 4).

Since the amino acid sequence is an inherent property of any protein it would have been *prima facie* obvious for one of skill in the art at the time the invention was made to synthesize and express the humanized chimera antibodies which bind to shiga toxins utilizing the methodology of Carter et al. One of ordinary skill in the art would have been motivated to humanize the monoclonal antibodies taught by Speirs et al. and O'Brien et al. in order to avoid the side effects by anti-mouse immunoglobulin antibody when said antibody is administered, yet still maintain an effective therapeutic effect. One would have had a high expectation of success since the process of humanizing a known antibody is well known in the art, particularly one directed to a human pathogen.

Claim Rejections Maintained

35 USC § 103

Claims 1, 2, 13-20, 23, 29 and 32-41 rejected under 35 U.S.C. 103(a) as being unpatentable over Speirs et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Shitara et al. (U.S. Patent 5,866,692) for the reasons outline in the rejection of claims 1, 2, 13-20, 23 and 29 in the previous Office action.

Applicant argues:

1. The cited documents fail to provide any amino acid or nucleic acid sequence information relating to a humanized anti-shiga toxin monoclonal antibody.

2. The aforementioned rejection is contradictory to the rejection made under the first paragraph of 35 U.S.C. 112.

3. The Federal Circuit has made it abundantly clear that not even the disclosure of a protein sequence renders a particular DNA obvious.

4. None of the references, either alone or in combination, teaches or suggests how to make or manipulate the DNA information furnished by Applicants. There would be no motivation to make Applicant's humanized monoclonal antibodies.

Applicant's arguments have been fully considered and deemed to be non-persuasive.

Speirs et al. disclose the use of the 11E10 monoclonal antibody that binds to shiga-toxin II and the 13C4 monoclonal antibody that binds verotoxin 1 (see abstract and page 651, first column).

O'Brien et al. also teach the use of 11E10 monoclonal antibody of the IgG1 subclass with a kappa light chain (see column 4, lines 10-19 and lines 38-58).

Neither Speirs et al. nor O'Brien et al. disclose the sequences (either DNA or amino acid) of the 13C4 or 11E10 monoclonal antibodies.

Shitara et al. disclose a method of producing humanized chimera antibodies. Said antibodies do not cause the formation of anti-mouse immunoglobulin antibody in the body of a patient and therefore side effects are reduced (see abstract and column 1, lines 10-48).

Since the amino acid sequence is an inherent property of any protein it would have been *prima facie* obvious for one of skill in the art at the time the invention was made to synthesize and express the humanized chimera antibodies which bind to shiga toxins using the methodology disclosed by Shitara et al. One of ordinary skill in the art would have been motivated to humanize the monoclonal antibodies taught by Speirs et al. and O'Brien et al. in order to avoid the side effects by anti-mouse immunoglobulin antibody when said antibody is administered, yet still maintain an effective therapeutic effect. One would have had a high expectation of success since the process of humanizing a known antibody is well known in the art, particularly one directed to a human pathogen.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., DNA sequences) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant invention is drawn to monoclonal antibodies with a given binding specificity not to nucleic acids.

In response to Applicant's argument that the aforementioned reference is in contradiction to the rejection made under the first paragraph of 35 U.S.C. 112, Applicant is reminded that the specification is enabled for the humanization of the 13C4 and 11E10 antibodies.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on M-Th 7:30 am - 5:00 pm and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner can be reached on (703) 308-1032. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman
September 4, 2002